EXHIBIT K

ARTICLES

Effects of preoperative warming on the incidence of wound infection after clean surgery: a randomised controlled trial

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Summary

Background Wound infection after clean surgery is an expensive and often underestimated cause of patient morbidity, and the benefits of using prophylactic antibiotics have not been proven. Warming patients during colorectal surgery has been shown to reduce infection rates. We aimed to assess whether warming patients before short duration, clean surgery would have the same effect.

Methods 421 patients having clean (breast, varicose vein, or hernia) surgery were randomly assigned to either a non-warmed (standard) group or one of two warmed groups (local and systemic). We applied warming for at least 30 min before surgery. Patients were followed up and masked outcome assessments made at 2 and 6 weeks.

Findings Analysis was done on an intention-to-treat basis. We identified 19 wound infections in 139 non-warmed patients (14%) but only 13 in 277 who received warming (5%; $p=0.001$). Wound scores were also significantly lower ($p=0.007$) in warmed patients. There was no significant difference in the development of haematomas or seromas after surgery but the non-warmed group were prescribed significantly more postoperative antibiotics ($p=0.002$)

Interpretation Warming patients before clean surgery seems to aid the prevention of postoperative wound infection. If applied according to the manufacturers guidelines these therapies have no known side-effects and might, with the support of further studies, provide an alternative to prophylactic antibiotics in this type of surgery.

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Introduction

Wound infection remains one of the most common causes of morbidity in the surgical patient despite advances in surgical practice and the widespread use of prophylactic antibiotics. The average cost of a surgical wound infection has proved difficult to estimate,[1] but hospital costs alone may be over £1500 per patient.[2,3] The costs of treatment after discharge from hospital, where most wound infections are now diagnosed,[4-6] or the cost to the patient in prescription charges, loss of earnings and a reduced quality of life, are rarely taken into account.

Clean surgery is defined as uninfected, operative surgery, where no inflammation is encountered and the respiratory, alimentary, and genitourinary tracts are not opened.[7] The importance of infection rates in clean surgery should not be underestimated as they might be seen as an indicator of quality and used to determine surgical performance.[8,9]

Most studies suggest that the infection rate in clean surgery is 5% or lower.[4,10-13] However, other studies have shown that if patients are followed up intensely for 6 weeks after surgery, and the definition of infection is not solely limited to the presence of a purulent discharge, then infection rates might be nearer 10%.[6,8,14]

Many factors have been shown to reduce the incidence of surgical wound infection, most of which are now part of best practice. The value of prophylactic antibiotics in clean–contaminated and contaminated surgery is not contentious but the benefits of prophylactic antibiotics in reducing wound infection rates after clean surgery remain unclear. Although it has been suggested that antibiotics are beneficial[15] this idea has not been supported by other studies.[14,16]

Animal and human studies have shown that intraoperative hypothermia increases the risk of wound infection.[17-19] Intraoperative hypothermia is likely to cause a reduction in peripheral circulation, which may increase tissue hypoxia and make the wound more susceptible to infection, even if contamination levels are low. The process of warming using a warm air blanket, to prevent hypothermia, is becoming common practice for most major surgery but the benefits of warming during clean surgical procedures, where surgery usually lasts less than an hour.

An alternative may be to warm patients before short duration, usually day case, surgery. We aimed to assess the use of a local warming device and a warm air blanket for the reduction of infection after clean wound surgery.

Patients and methods

We did a randomised controlled trial to investigate the effects of preoperative warming using a local warming device and a warm air blanket on postoperative wound infection rates after clean surgery. We obtained local research ethics committee approval and informed consent from all patients. All data collection took place within the same district general hospital.

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Sample

An initial two sided calculation with 90% power estimated that a sample size of 402 (134 in each of the three groups) would be required to detect a significant reduction, at the 5% level, in either of the two warmed groups compared with the non-warmed group. Patients were judged eligible if they were having an elective hernia repair, varicose vein surgery, or breast surgery that would result in a scar longer than 3 cm in length. We excluded patients if they were under the age of 18 years, pregnant, were taking long-term oral steroids, had received radiotherapy (to the incision site) or chemotherapy in the last 4 weeks, or had an infection at the time of surgery.

Most patients were recruited to the study on the same day as surgery and randomly assigned to one of three groups, two intervention groups, systemic or local warming, and one non-warming (standard) group. Randomisation was prepared in blocks of 90, with the treatment allocation concealed in opaque envelopes.

Treatment

Patients randomly assigned to the non-warmed (standard) group received the usual preoperative care, which does not include any active temperature control.

Patients in the systemic warming group received the same standard preoperative care, plus the addition of a minimum 30 min preoperative warming to the whole body using a forced-air, warming blanket. Patients assigned to the local warming group also received the standard care and a minimum 30 min preoperative warming to just the planned wound area using a non-contact, radiant heat dressing. A research registrar (BA) and operating theatre nursing staff applied the warming devices before surgery. Both warming devices were left in situ until just before surgery.

Data collection and postoperative surveillance

We recorded demographics and patients' health profiles. Variables which have been shown to affect the rate of infection, such as skin preparation, length of operation, administration of prophylactic antibiotics, and experience of the operating surgeon were also recorded. Core temperatures were recorded (using tympanic thermometers calibrated according to manufacturers guidelines) before any treatment, after any warming, and after surgery.
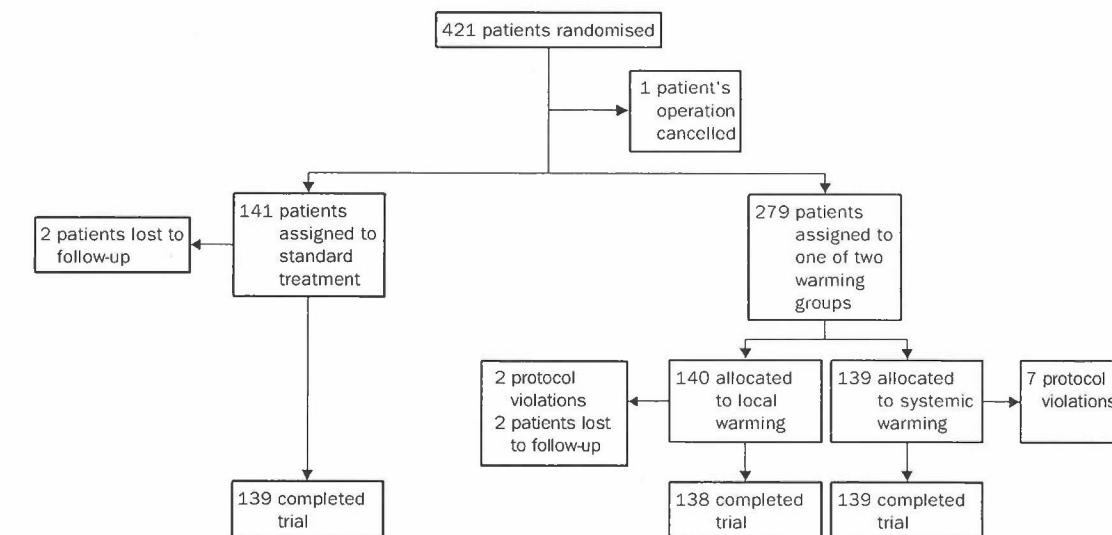
A single trained observer (ACM) who was unaware of treatment allocation reviewed patients at 2 and 6 weeks postoperatively in an outpatient clinic or their own homes. He observed wounds directly and interviewed patients briefly about their wound history. A patient diary, designed for the project was given to all patients and aided the process of wound surveillance. Wounds were swabbed for microbiological analysis if a purulent discharge was present at time of review.

We classified wounds as infected if there had been a purulent discharge or a painful erythema that lasted for 5 days and was treated with antibiotics within 6 weeks of surgery. All wounds were also scored using an adapted version of the ASEPSIS[20] wound scoring system. In a small number of cases, when patients were unable or unwilling to be seen at 6 weeks, a standardised telephone assessment was done, and a patient questionnaire was sent to the patient for completion. We distributed ten questionnaires, six of which were returned.

Statistical analysis

Analysis was carried out on an intention-to-treat basis using the statistical package for social sciences (SPSS, version 8). The effects of preoperative warming on primary outcomes (wound infection, ASEPSIS score, haematoma, seroma, wound aspiration, and postoperative antibiotics) were tested by combining the systemic and local warming groups into one warmed group, which was then compared with the non-warmed group using a two-tailed Pearson χ^2 test. We also individually compared the two warming groups with the non-warmed group (two-tailed Pearson χ^2 test) and then compared them with each other in the same way to identify any differences in outcome between the two. Absolute risk reduction was calculated by subtracting the rate of infection in the experimental group from the rate of infection in the control group. The reciprocal of this was then taken to give the numbers needed to treat.[21]

The effect that other variables (table 4) had on the presence of infection was tested using logistic regression. Initial univariate analysis with a two-tailed Pearson χ^2 test and paired or non-paired t tests were used to identify

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Trial profile

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Characteristics	Standard (n=139)	Systemic warming (n=139)	Local warming (n=138)
Age (years)*	50·4 (15·3)	49·7 (13·7)	50 (14·1)
Body mass index*	25·6 (4·1)	25·7 (4·3)	25·8 (4·1)
Sex			
Male	55 (40%)	64 (46%)	55 (40%)
Female	84 (60%)	75 (54%)	83 (60%)
Fasted for more than 8 h	44 (32%)	43 (31%)	47 (34%)
Incision site shaved more than 6 h before surgery	67 (48%)	54 (39%)	74 (54%)
Type of surgery			
Breast	60 (43%)	57 (41%)	58 (42%)
Hernia	47 (34%)	54 (39%)	54 (39%)
Varicose veins	32 (23%)	28 (20%)	26 (19%)
Previous surgery (in the last 3 months)	5 (4%)	6 (4%)	6 (44%)
Cancer diagnosis	42 (30%)	37 (27%)	38 (28%)
Initial core temperature (˚C)*†	36·5 (0·55)	36·67 (0·49)	36·64 (0·53)
Prophylactic antibiotics	47 (34%)	36 (26%)	36 (26%)
Length of surgery (min)*	48 (17·52)	49·3 (15·63)	49·5 (19)
Seniority of surgeon (42)‡			
Senior house officer	12 (9%)	11 (9%)	11 (9%)
Registrar	47 (37%)	51 (42%)	55 (45%)
Consultant	70 (50%)	61 (50%)	56 (46%)

*Values are mean (SD). †Initial core temperature was recorded on admission to the day case unit or on the surgical ward before transfer to theatre. ‡Data missing for 42 patients.

Table 1: **Characteristics of the patients in the three treatment groups**

Outcome	Local warming	Systemic warming	All warmed patients	Non-warmed patients	p*
Wound infection	5 (4%)	8 (6%)	13 (5%)	19 (14%)	0·001
ASEPSIS score					
0–10	130 (94%)	129 (93%)	259 (94%)	115 (83%)	
11–20	4 (3%)	4 (3%)	8 (3%)	7 (5%)	
21–30	3 (2%)	3 (2%)	6 (2%)	9 (7%)	
31–40	1 (0·7%)	1 (0·7%)	2 (0·7%)	6 (4%)	
>41	0	2 (1%)	2 (0·7%)	2 (1%)	0·007
Haematoma	4 (3%)	2 (1%)	6 (2%)	5 (4%)	0·26
Seroma	7 (5%)	4 (3%)	11 (4%)	8 (6%)	0·41
Wound aspirated	7 (5%)	4 (3%)	11 (4%)	9 (7%)	0·27
Prescribed postoperative antibiotics	9 (7%)	9 (7%)	18 (7%)	22 (16%)	0·002

*Calculated by comparing warmed patients with non-warmed patients.

Table 2: **Postoperative outcomes**

candidate variables to enter a backwards stepwise logistic regression. The criteria for selecting candidate variables was p<0·25.[22]

Results

From April, 1999, to May, 2000, 421 patients were recruited into the study (figure). One patient randomly assigned to local warming had his operation cancelled and four patients (two local warming and two standard) were lost to follow-up, leaving 416 patient data sets for further analysis.

139 patients received standard treatment, 138 received local warming, and 139 received systemic warming. Nine protocol violations occurred, all in the warming groups. These were mainly due to logistical problems—eg, a change in operating times made warming impossible—or an unexplained pyrexia, where a clinical decision was made not to warm.

The characteristics of the three randomisation groups were similar (table 1). Core temperatures were significantly increased by both local warming (mean 0·13 ˚C [SD 0·57], p=0·028) and systemic warming (0·35°C [0·58], p=0·001). The mean core temperature after surgery was within normal limits (36·41°C [0·59]). Patients who were assigned to the local warming group received a significantly longer period of warming than the systemic warming group (44·94 *vs* 38·73 min, p=0·005).

The overall rate of surgical wound infection was 8%. There was a lower rate of wound infection in the

combined warming group when compared with the group of patients who were not warmed (p=0·001). ASEPSIS wound scores were also significantly lower (p=0·007) in the warmed group compared with the non-warmed group (table 2).

Individually both systemic warming (p=0·026) and local warming (p=0·003) had a significant effect on the rate of wound infection. Table 3 shows the absolute risk reductions and numbers need to treat. Less wound infections were reported in patients who were locally warmed compared with those in the systemically warmed group, however, this was not significant (p=0·4).

Preoperative warming did not significantly reduce other wound complications such as haematoma, seroma, and wounds requiring aspiration (table 2). However, less patients who were warmed were given postoperative antibiotics than those who received no warming (p=0·002; table 2). Ten positive and four negative wound swabs were obtained. *Staphylococcus aureus* was the most commonly cultured organism (n=8).

	Systemic warming	Local warming
Absolute risk reduction (95% CI)	7·9% (1·0–14·8)	10·1% (3·6–16·6)
Relative risk reduction	57·7%	73·7%
Numbers needed to treat relative to the standard treatment	15 patients	10 patients

Table 3: **The effects of warming therapies compared with standard treatment**

	Wound infection (n=32)	Non-wound infection (n=384)
Age (years)*	48·06 (13·47)	49·96 (14·48)
Body mass index (kg)*	28·04 (5·44)	25·51 (3·98)
Male/female	12/20	162/222
Smokers	11 (34%)	118 (31%)
Type of surgery		
Breast	18 (56%)	157 (41%)
Hernia	10 (31%)	145 (38%)
Varicose veins	4 (13%)	82 (21%)
Previous surgery (in the last 3 months)	3 (9%)	29 (8%)
Cancer diagnosis	11 (34%)	106 (28%)
Shaving times†		
Didn't shave	9 (28%)	101 (27%)
Within 7 h	6 (19%)	110 (30%)
7 h or more	17 (53%)	166 (44%)
Fasting times‡		
8 h or less	23 (72%)	250 (67%)
More than 8 h	9 (28%)	125 (33%)
Theatre		
Day case unit	30 (94%)	330 (86%)
Main theatre	2 (6%)	54 (14%)
Initial core temperature (˚C)*	36·7 (0·55)	36·6 (0·53)
Postwarming temperature (˚C)*	36·9 (0·28)	36·9 (0·58)
Postoperative temperature (˚C)*	36·6 (0·66)	36·4 (0·59)
Prophylactic antibiotics	6 (19%)	115 (30%)
Operation time*	51·3 (18·5)	48·69 (17·4)
Seniority of surgeon§		
Senior house officer	12 (38%)	175 (51%)
Registrar	17 (53%)	136 (40%)
Consultant	3 (9%)	31 (9%)

*Values are mean (SD). †Data missing for seven patients. ‡Data missing for nine patients. §Data missing for 42 patients.

Table 4: **Characteristics of patient by wound infection**

Breast surgery had a higher wound infection rate than hernia surgery and varicose vein surgery (table 4). Stepwise logistic regression of the data in table 4 yielded only body mass index as a significant variable at the 5% level, with an odds ratio of 1·12 (95% CI 1·02–1·21)

Discussion

All surgical patients are at risk of a wound infection and this risk increases if tissue perfusion is poor after surgery.[23] We have shown that a 30 min period of warming, before surgery, reduces infection rates from 14% to 5%. The length of surgery was short and core temperatures in the recovery room do not suggest that patients were hypothermic. However, due to the whole surgical episode of preoperative anxiety, prolonged fasting, anaesthetic drugs, and surgery our patients are still likely to have had reduced peripheral circulation before, during and immediately after surgery. A previous study[24] done on healthy volunteers showed that tissue oxgen partial pressure can be increased by local radiant heating, which persisted for 3 h after removal. If applied, as in this study, before short duration surgery the 3 h of increased partial pressure of oxygen could be long enough to sustain the patient's host defences through the decisive period where infection is most likely to become established.[25]

The high wound infection rate in the standard group compares with other studies where follow-up, by a trained, unbiased observer, was intense and wound scoring was used.[6,8,14] Only 14 wound swabs were obtained in this current study. There are several reasons for this low figure, but the most important was that patients who were seen at 2 and 6 weeks had often been prescribed antibiotic treatment by their general practitioner without having their wounds swabbed. This

may also account for three of the four negative swab results. *S aureus* was the most common organism grown and reflects the findings of previous studies on similar patients.[12,14,15]

Prewarming patients, if applied according to the manufacturers' guidelines, appears to have no adverse side-effects. Initial concerns were raised by some surgeons, who felt that patients bled more at the beginning of their operations. However, this does not appear to have caused any complications as the warmed patients had a lower rate of haematoma and seroma development.

We did not show any differences in outcome between the two types of warming. Although local warming resulted in fewer infections than systemic warming, this difference was not significant. Both methods, increased core temperature by a significant amount, however, the patients in the local warming group were warmed for significantly longer periods than the systemic warming group. This discrepancy was probably due to local warming not relying upon a mains supply, which meant it could be transported with the patient and remain in place until skin preparation.

Despite the findings of other studies only a higher body mass index was shown to significantly increase the patients risk of developing a wound infection.[26] Other recognised risk factors, such as age,[11,13,26] shaving,[10,27] and length of operation[10,11] had little effect.

The surgical episode and the first few hours afterwards have been widely accepted as the key period when a wound infection is likely to become established.[25] This paper suggests that the hour before surgery may be just as important. The simple addition of two different types of warming, applied for at least 30 min before surgery, have both clearly reduced infection rates and therefore the need for additional treatment, including postoperative antibiotics.

Preoperative warming may be an alternative to the controversial use of prophylactic antibiotics,[14–16] that avoids the associated risks of allergy and resistance, in clean surgery.

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